Review of: "Harnessing secretory pathway differences between HEK293 and CHO to rescue production of difficult to express proteins"

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Providing human recombinant proteins for large scale production is one of the main themes of biopharmaceutics. This study compared CHO (the cell line commonly used to produce recombinant proteins) and HEK293 productivity and secretion ability of human recombinant proteins. They evaluated, the expression systems for production of a set of human difficult to express secreted proteins or extracellular domains of single-pass plasma membrane-anchored proteins. Interestingly, one third of the challenging human proteins displayed improved secretion upon host cell swapping from CHO to HEK293. To uncover this different secretion efficiency, they compared the transcriptome of secretory pathways components between cell lines. While most components of the secretory machinery showed comparable expression levels in both expression hosts, genes with significant expression variation were identified. Among these, ATF4, SRP9, JUN, PDIA3 and HSPA8 were validated as productivity boosters in CHO observing their overexpression in this cell line improved the secretion on recombinant proteins. To conclude they coupled post-translational modifications (glycosylation in particular) with the protein titer improvements from CHO to HEK293. They observed the titer improvement for more heavily glycosylated proteins showed a strong positive correlation with the differential expression of glycosyltransferases which is expressed the most in HEK293 cell line.

As reported by the authors HEK293 cells are easier to transfect and express higher levels of recombinant proteins than CHO. Therefore, the study to assess the net contributes of secretory pathways could remove the impact of protein synthesis machinery using for example cycloheximide treatments. In this way should be possible to observe the lone effect of the secretory pathways on the secretion of human recombinant proteins.

As stated by the authors in the discussion the different transcriptomic profile of secretory pathways elements can rely on two possibilities: “Since the r-proteins in our screen are all human proteins, it is possible that the lack of compatible secretory components forced the CHO cells to utilize a smaller subset of more generic machinery components, and this lack of specialization could possibly impact secreted titers. Alternatively, the

absence of expression of such genes in CHO may be compensated by the expression of other genes without a human ortholog and hence not included in our analysis". Therefore, it is crucial to define this point following the secretory route of human recombinant proteins differently secreted by the two cell lines (using fluorescent proteins, live imaging and exosome fractionation to better characterize these secretory pathways).

The different production efficiency of human recombinant protein can be ascribable not only to specie-specific protein synthesis and secretion pathways but also to tissue specific pathways. The authors could include other murine and human cell lines from different source tissue to study the impact of tissue specific machinery on the production of human recombinant proteins.